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EXAMINER	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,318	FEINBERG, ANDREW P.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive to the amendment and terminal disclaimer filed August 22, 2007, the complying supplemental amendment filed January 31, 2008, and the Response to Restriction Requirement filed December 26, 2008. In the amendment filed August 24, 2007, claims 1, 7-8, 10, 17, and 20 were amended and claim 19 was canceled. In the amendment filed January 31, 2008, claim 7 was amended. As was indicated in the supplemental Election/Restriction mailed October 29, 2008, claims 9 and 12 have been rejoined. Accordingly, **the current status of the claims is as follows**: claims 1-18 and 20 are under consideration, and claim 21 remains withdrawn.

Upon further consideration, and in view of the amendment of each of the independent claims to require a correlation between hypomethylation and loss of imprinting (LOI), the claims are rejected on the new grounds set forth below. Applicant's arguments have been thoroughly reviewed but are moot in view of the new grounds of rejection. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is NON-FINAL.**

Election/Restrictions

2. Applicant's further election of SEQ ID NOS 2 and 3 (as set forth in claim 9) in the reply filed on December 26, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. It is noted that applicant's election was responsive to the supplemental Election/Restriction mailed October 29, 2008, which was necessitated by the rejoinder

of claims 9 and 12 (see the Election/Restriction mailed October 29, 2008). However, it is again noted that the amended claims have now been rejected on new grounds. As there is no allowable generic claim, examination presently remains limited to the elected species.

Terminal Disclaimer

4. The terminal disclaimer filed on August 24, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on application no. 10/336,552 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim1-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "hypomethylation" in each of independent claims 1, 10 and 17 (and throughout the claims) is a relative term which renders the claim indefinite. The term "hypomethylation" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. With further regard to the specification, page 13, paragraph 42 states that "Hypomethylation of a DMR is present when there is measurable decrease in methylation of the DMR"; however, it is not clear

with respect to what the decrease is to be measured (i.e., what type of standard or control, or other type of sample, is used for purposes of determining that a decrease in methylation is present?). The specification further provides an example in paragraph 42 stating that "the H19 DMR can be determined to be hypomethylated when it is methylated at less than 10, less than 5, or less than 3 sites of all of the greater than 25 methylation sites within the H19 DMR". Thus, it is clear that a variety of different thresholds may be employed in determining that 'hypomethylation" is present; however, it is not clear which of these standards applies to the present claims. As a result, it would not be clear to one of skill in the art how "hypomethylation" is determined to be present, and it is therefore also not clear what types of methods would/would not infringe applicant's claims. Accordingly, clarification is required.

Claim 14 is indefinite over the recitation of the term "corresponds to" in the claim. The claim references a DMR that "corresponds to SEQ ID NO: 1 or a polymorphism thereof". However, neither the specification nor the prior art provide any kind of clear, limiting definition of this term, as would be necessary for one of skill in the art to recognize what types of molecules are (and are not) embraced by the claims. Accordingly, the use of the term "corresponds to" renders the claim indefinite.

Claim 20 is indefinite because it is not clear how the claim further limits claim 17, from which it now depends. Independent claim 17 requires analyzing a sample from a subject for "hypomethylation of a IGF2 gene," and makes no mention of H19. However, claim 20 indicates that hypomethylation is analyzed for "at least one of" an H19 DMR or an IGF2 DMR. The language of the claim does not make clear how analyzing an H19

DMR for hypomethylation relates back to claim 20, either with respect to analysis of IGF2 gene hypomethylation or in any other way. Accordingly, clarification is required.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which a biallelic absence of methylation at positions 87, 90, and 106 of SEQ ID NO: 1 is detected in human blood or colonic mucosa samples as correlating with LOI of the IGF2 gene in human colorectal cancer (CRC) patients and as an indicator of CRC risk in human subjects, does not reasonably provide enablement for methods employing detection of any other type of "hypomethylation" within the H19 and/or IGF2 genes (including any sequences of SEQ ID NO 6 or a "polymorphism thereof" or other nucleotides within SEQ ID NO: 1 or "polymorphisms" thereof) as indicators of LOI of H19 and/or IGF2 or as indicators of cancer risk (including CRC risk), or for the use of any other types of samples or practice of methods in other types of subjects (i.e., any non-human subjects), or for detection of risk for any other type of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-9 are drawn to methods for "identifying loss of imprinting (LOI) of the IGF2 gene in a subject with colorectal cancer" comprising "analyzing a biological sample from the subject for hypomethylation of a differentially methylated region (DMR) of at least one of the H19 gene and the IGF2 gene and detecting hypomethylation of the DMR in the subject, wherein detection of hypomethylation of the DMR in the subject correlates with" LOI. Claims 2, 5, and 9 further specify that the DMR is present in an IGF2 gene comprising SEQ ID NO: 1 or "a polymorphism thereof" or a fragment of SEQ ID NO: 1 "or a polymorphism thereof" (claim 2); with claim 5 further limiting the IGF2 gene to SEQ ID NO: 1, while claim 9 requires the use of a particular primer pair in the analysis (of which SEQ ID NOs 2 and 3 have now been elected). Claims 3 and 6-8 further specify that the DMR is present in an H19 gene comprising SEQ ID NO: 6 or "a polymorphism thereof" or a fragment of SEQ ID NO: 6 "or a polymorphism thereof" (claim 3); claim 6 further limits the H19 gene to SEQ ID NO: 6, claim 7 further limits the DMR to a DMR "comprising a CTCF binding site" wherein the site comprises nucleotides 3010-3172 of SEQ ID NO: 6, and claim 8 further requires the use a

particular primer pair (SEQ ID NOs 23-24). Claim 4 further requires analysis of both a DMR of the H19 gene and a DMR of the IGF2 gene for hypomethylation. Thus, claims 1-9 encompass the detection of hypomethylation at a vast number of locations throughout the IGF2 and/or H19 genes (and variants thereof) as an indicator of LOI in a colorectal cancer (CRC) patient. It is further noted that the claims encompass the analysis of any type of biological sample, and the subject analyzed may be any mammalian organism with CRC (see paragraph 68 at page 21).

Claims 10-16 are drawn to methods of "identifying an increased risk of developing cancer in a human subject" comprising "analyzing a biological sample for the subject for hypomethylation of" a DMR of an H19 gene or an IGF2 gene, wherein "detection of hypomethylation of the DMR in the subject correlates with" LOI, and wherein LOI "is indicative of increased risk of the subject developing cancer". Claim 11 further limits the cancer to CRC. Claim 12 requires the use of the primer pairs SEQ ID NOS 23-24 and SEQ ID NOS 25-26. Claim 13 limits the subject to a subject not known to have a colorectal neoplasm. Claim 14 further specifies that the "H19 DMR" comprises SEQ ID NO: 6 or "a polymorphism thereof" or a fragment of SEQ ID NO: 6 "or a polymorphism thereof" , and that the IGF2 DMR "corresponds to" SEQ ID NO: 1 or a polymorphism thereof, or a fragment of SEQ ID NO: 1 or a polymorphism thereof. Claim 15 further requires analysis of both a DMR of the H19 gene and a DMR of the IGF2 gene for hypomethylation. Claim 16 further limits the biological sample to a blood sample. Thus, claims 10-16 also encompass the detection of hypomethylation at a vast number of locations throughout the IGF2 and/or H19 genes (and variants thereof) as an

indicator of LOI, and additionally, as an indicator of increased cancer risk in any type of human subject. It is further noted that the claims (other than claim 16) encompass the analysis of any type of biological sample.

Claims 17-18 and 20 are drawn to a method for "identifying an increased risk of developing cancer in a subject" comprising "analyzing a first genomic DNA sample from the subject for hypomethylation of a IGF2 gene, wherein hypomethylation of the IGF2 gene correlates with the loss of imprinting of the IGF2 gene, and wherein a loss of imprinting of the IGF2 gene is indicative of an increased risk of developing cancer, thereby identifying an increased risk of developing cancer in the subject". Claim 18 further limits the cancer to CRC. Claim 20 further specifies that hypomethylation is "analyzed for at least one of" an "H19 DMR" comprising SEQ ID NO: 6 or "a polymorphism thereof" or a fragment of SEQ ID NO: 6 "or a polymorphism thereof" , and an IGF2 DMR comprising SEQ ID NO: 1 or a polymorphism thereof, or a fragment of SEQ ID NO: 1 or a polymorphism thereof. Accordingly, claims 17-18 and 20 encompass the detection of hypomethylation at a vast number of locations throughout the IGF2 and/or H19 genes (and variants thereof) as an indicator of LOI of the IGF2 gene, and additionally, as an indicator of increased cancer risk in any type of mammalian subject. The claims also encompass the analysis of any type of biological sample.

It is unpredictable as to whether one of skill in the relevant art could actually use applicant's invention as claimed. Claim 1 and claims dependent therefrom require that one be able to detect hypomethylation at essentially any location throughout the IGF2

and/or H19 genes, or variant forms thereof, as an indicator of LOI of IGF2 in any CRC subject. Claim 10 and claims dependent therefrom require that one be able to detect hypomethylation at essentially any location throughout the IGF2 and/or H19 genes, or variant forms thereof, as an indicator of both LOI of IGF2 and of increased cancer risk in any human subject. Finally, claim 17 and claims dependent therefrom require that one be able to detect hypomethylation at essentially any location throughout the IGF2 and/or H19 genes, or variant forms thereof, as an indicator of both LOI of IGF2 and of increased cancer risk in any mammalian subject. In evaluating the enablement of the claims, the teachings of the specification and of the prior art have been considered as discussed below.

The specification provides 2 examples. **Example 1** is described as illustrating "that LOI in normal tissue is associated with either a family history or personal history of colorectal neoplasia" (see page 45). Colon tissue samples and peripheral blood lymphocytes (PBLs) were collected from 421 patients, of which 191 were found to be informative for polymorphisms allowing determination of imprinting status (see page 48, paragraph 163). Imprinting status was determined quantitatively by RT-PCR of RNA (see page 46, par 156), and no significant relationship between LOI and age, sex or race was identified (par 164, page 49). The specification states that the "odds of LOI in PBL were 4.4 times greater in patients with a positive family history of CRC compared to their counterparts with a negative family history ($p = 0.003$; Table 1)" (page 49, par 164). The specification also reports that the "odds of LOI in PBL were 4.4 times greater in patients with past or present colorectal neoplasia (adenomatous polyps or cancer)

than their counterparts without neoplasia (p=0.002; Table 1), indicating a strong association between LOI and colorectal neoplasia" (par 165, page 49). The specification also reports odds 4.7 times greater when patients with a positive family history are excluded (0=0.01), as well as stratified odds of LOI that are "4.1 times greater in patients with past or present adenomas but no CRC, compared to patients with no past or present neoplasia (p=0.016; Table 1)" and "34.4 fold greater in patients with past or present CRC than in those without colorectal neoplasia (p<0.0001; Table 1)", stating that these latter findings "strongly suggest that LOI is associated with both initiation and progression of colorectal neoplasia" (page 49, par 165 and 166). However, at page 51 (par 167), applicant reports that while all patients with LOI in PBL "also showed LOI in normal colon," other patients exhibited LOI only in the colon, and that in these patients "no statistically significant association with family or personal history of colorectal neoplasia was found". Thus, applicant's above noted findings regarding an association between LOI and initiation and/or progression of CRC pertain to those patients exhibiting LOI in PBL, but not those exhibiting LOI in colon tissues. Rather, it appears in Example 1 that no conclusions with regard to CRC may be drawn based on a finding of LOI in colon tissue samples. The specification also reports analysis of the methylation status of DNA at 3 positions in the IGF2 DMR located upstream of exon 3, corresponding to positions 87, 90 and 106 of instant SEQ ID NO: 1 (see page 47). Applicants assaying a total of 24 samples from 12 patients "without known neoplasia", 6 PBL and 6 matched normal colonic mucosa samples having normal imprinting, and 6 PBL and 6 matched normal colonic mucosa samples with LOI

(page 51, par 168). The specification reports that the 12 samples with normal imprinting showed a "normal pattern of half-methylation (Fig 1A)" of IGF2, while 11 of the other 12 samples with LOI showed hypomethylation of the IGF2 DMR" with the 12th sample showing abnormal partial methylation of both alleles, referencing Fig. 1B (page 51, par 168). Applicants report that the difference between normal and LOI tissues was significant, with a p value < 0.0001 (page 52, par 168)". With regard to methylation analysis, the specification also teaches that "H19 showed hypomethylation in all cases, regardless of imprinting status," indicating that no association was found between LOI and methylation status of the H19 gene in the assays of example 1. Thus, the data of Example 1 is sufficient to establish an association between a biallelic absence of methylation at the 3 particular bases of the IGF2 gene analyzed and LOI of IGF2 in colon tissues and PBL, as well as an association between CRC in human subjects and LOI of IGF2 in PBLs. **Example 2** is described as illustrating "that loss of imprinting of IGF2 in colorectal cancer is correlated with hypomethylation of the DMR of IGF2, and in at least some colorectal cancer patients with hypomethylation of the DMR of H19" (page 53, par 172). Applicants disclose the use of bisulfite sequencing analysis to determine methylation of the IGF2 DMR sequence as well as CTCF binding site 1 (CBS1) of the H19 gene (see page 53, pars 173 and 174) in both knockout cell lines and primary CRCs (see pages 54-57). The specification discloses that both the H19 and IGF2 DMRs were found to be hypomethylated in 3 genetically engineered cell lines exhibiting IGF2 LOI (see par 177 and Table 3). However, the specification provides no evidence that the cell lines examined are, e.g., accepted models of human disease and/or human

LOI of IGF2, or otherwise establish that the findings in these particular cells are in some way representative of disease mechanisms that occur *in vivo*, nor is such evidence provided by the prior art. The specification further teaches the analysis of 20 primary CRC specimens informative for LOI of IGF2, of which 12 exhibited LOI and 8 exhibited normal imprinting (par 178). The specification reports that all 12 CRCs with LOI exhibited hypomethylation of the IGF2 DMR (p= 0.000007) and that all 8 CRCs with normal imprinting showed normal half-methylation of the IGF2 DMR. The specification also states that "We also observed hypomethylation of the H19 DMR in CRC, although the differences were not absolute as in the case of the IGF2 DMR" (par 178, Table 4). An inspection of Table 4 reveals that H19 methylation status at CBS1 and CBS6 in the samples exhibiting LOI of IGF2 is hypomethylated in some cases and (normal) half methylation in other cases, and the specification provides no evidence of a statistically significant association between hypomethylation of any H19 DMR and IGF2 LOI (or CRC or any other cancer). Thus, the data of Example 2 support an association between LOI and a biallelic lack of methylation of the IGF2 gene at the specific positions analyzed by applicants in primary CRC samples. Accordingly, given the guidance in the specification, one of skill in the relevant art would recognize a correlation between LOI of IGF2 and an absence of methylation at these positions, and would reasonably consider the detection of such hypomethylation/LOI in colonic mucosa and/or PBLs of a human subject as one factor indicating a possible increased risk for CRC in a human subject. With regard to the elected primer pair of SEQ ID NOS 2-3, it is further noted that the specification demonstrates the successful use of this primer pair in the analysis

of positions 87, 90, and 106 of SEQ ID NO: 1 for methylation status (see, e.g., page 47 of the specification). However, while the specification also exemplifies the use of primer pairs 23-24 and 25-26 in analyzing H19 gene methylation status (see page 53), the specification does not demonstrate that detection of methylation within this region is relevant to detection of IGF2 gene LOI and/or cancer (as discussed above).

While the claims require a correlation between LOI of IGF2 and any type of hypomethylation of IGF2 and/or H19, no such association is actually established in the specification. Rather, the examples in the specification provide evidence that a total lack of methylation at 3 particular sites in the IGF2 DMR described above is associated with LOI of the IGF2 gene in human CRC patients, and further that this type of LOI is association with CRC. Evidence is lacking in the specification with regard to: a) an association between hypomethylation of any other type and at any other locations within IGF2 (or any "polymorphism thereof") and LOI and/or any type of cancer; b) an association between hypomethylation of any locations in the H19 gene (or any polymorphism thereof) and LOI of IGF2 and/or H19, as well as with any type of cancer; and c) successful detection of hypomethylation of the 3 particular sites within the IGF2 gene as an indicator or LOI and/or cancer in any sample type other than blood or colon tissues. Further, the specification provides no data or evidence indicating that the invention is enabled for use with other cancer types or other types of subjects; applicant exemplifies only the practice of the invention as discussed above in human subjects having a particular type of cancer (colorectal cancer).

Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance with regard to enablement of a claimed invention. However, in the present case the teachings of the prior art do not provide further enabling guidance with regard to the claimed invention. Regarding claim 1 and claims dependent therefrom (i.e., the claims requiring a correlation between hypomethylation of IGF2 and/or H19 genes and LOI of IGF2 in a subject with CRC), the prior art as exemplified by Cui et al (Nature Medicine 4(11):1276-1280 [Nov 1998]) discloses that LOI of IGF2 was observed in tumor and matched normal colonic mucosa samples in 12 of 27 CRC patients, and in PBL samples of 4 of those patients, whereas 2 of 16 control patients exhibited LOI of IGF2 in normal colonic mucosa, and 2 of 15 patients in PBLs (see entire reference). However, neither Cui et al nor the prior art as a whole establishes hypomethylation of either IGF2 and/or H19 as correlating with LOI of IGF2 in CRC patients, as is required by the claims. Further, Nakagawa et al (PNAS 98(2):591-596 [January 2001]) teach that at least one location with the H19 gene is hypermethylated in CRC patients exhibiting LOI of IGF2 (see entire reference, particularly pages 594-595), indicating that an opposite methylation pattern in H19 is associated with IGF2 LOI and CRC in human patients. With particular regard to claims 10 and 17 and claims dependent therefrom (i.e., those claims requiring both a correlation between LOI and hypomethylation and an association with cancer risk), the closest prior art reference, Ahomadegbe et al (Proceedings of the National Association for Cancer Research Annual Meeting, Vol. 37, p. 598 [April 1996]), discloses the analysis of both LOI and methylation status of IGF2 and H19 genes in two types of

invasive breast carcinomas (see entire abstract); however, while Ahomadegbe et al report that both genes are "highly hypomethylated" and that LOI was observed in some samples (6 of 15 inflammatory breast cancers and 1 of 6 non-inflammatory breast cancers), the references teaches that the genes were highly hypomethylated "whatever their LOI status." Thus, Ahomadegbe et al do not teach or suggest the existence of a correlation between hypomethylation and LOI in cancer (as is set forth in the present claims). Furthermore, the post-filing date reference of Ito et al (Human Molecular Genetics 17(17):2633-2643 [June 2008]) teaches that further study of IGF2 methylation in association with LOI and various cancers revealed that IGF2 hypomethylation is "highly prevalent" in cancer but is independent of imprinting/LOI (see entire reference, particularly page 2634, right column). It is also particularly noted that Ito et al reference the publication of Cui et al (reference "15") that corresponds to the provisional application of which the present application claims the benefit, and concludes that hypomethylation of DMRO of IGF2 is "not invariably associated" with LOI (page 2636, right column), and further that hypomethylation at this site is also "acquired in peripheral blood with age, but does not predict further risk for breast or colorectal cancer" (see page 2638). Additionally, the post-filing date reference of Jirtle et al (Gastroenterology 126:1190-1201 [April 2004]) teaches that only hypomethylation of DMRO of IGF2 has been found to be "tightly linked with IGF2 loss of imprinting in CRC" (see entire reference, particularly page 1191, bottom of left column). Thus, the teachings of the art as a whole support a conclusion that only a very specific type of hypomethylation related to LOI of IGF2 is associated with human CRC. Finally, with regard to subjects

other than non-human subjects, it is noted that the art (like the specification) does not provide evidence of an association between hypomethylation of IGF2 and/or H19 genes and LOI of IGF2 and/or cancer, and that the prior art as exemplified by Jinno et al (Human Molecular Genetics 5(8):1155-1161 [1996]) emphasizes the structural differences (rather than any commonalities) between human and mouse H19 loci (see entire reference). Thus, in the present case, the teachings of the prior art do not support further or broader enablement of the invention claimed. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct further experimentation aimed at determining whether applicant's methods may be successfully employed with respect to, e.g., other cancer types, other types of subjects, etc. However, the outcome of such experimentation is entirely unpredictable, and it is unknown as to whether any quantity of experimentation – even an infinite amount – would be sufficient to identify other enabled embodiments embraced by the claims. Such a quantity and type of experimentation is clearly undue. Accordingly, while the specification is enabling with regard to methods in which a biallelic absence of methylation at positions 87, 90, and 106 of SEQ ID NO: 1 is detected in human blood or colonic mucosa samples as correlating with LOI of the IGF2 gene in human subjects and as an indicator of CRC risk in such subjects, it would require undue experimentation to use applicant's invention in a manner commensurate with the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571/272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634